

On being rare

The good news is that rare adverse events don't happen very often. The bad news is that rare events don't happen very often, and that the rare adverse events that we want to know about are bad, significant, and usually irreversible.

It is the rarity of rare events that makes them hard to identify, and it is harder still to measure their frequency with any accuracy. This issue of Bandolier looks at a number of examples of rare adverse events to explore the point. Examples come from cohort studies, from case-control studies, and from a long-term follow up of a randomised trial.

All share the same problem, that the number of events of interest is small, even in large studies. The number of cases of interest varied from eight to 24 in total, despite huge cohorts, or large numbers of cases in case-control studies. We find ourselves worrying about whether there are sufficient numbers to avoid chance findings.

How much we worry depends to some extent on how statistically significant an effect is. Large relative risks or odds ratios might be real despite small numbers. Small relative risks are more of a worry, especially when we find that biases can and do occur in observational studies. Where relative risks or odds ratios are close to 1, unknown biases are likely to make a difference, but not when they are far from 1.

Bandolier has no formula that can be applied universally to studies of rare events to tell whether a particular result is true or not. But it does have a rule of thumb it is working to perfect:

- Large studies, or pooled analyses of smaller studies, with lots of events, and big differences are probably about right.
- Bare statistical significance, or small effects, or small numbers, suggest caution is necessary.

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RHABDOMYOLYSIS WITH STATINS

That muscle problems can occur with statins and other lipid lowering drugs is an accepted problem. While some people seem unable to take statins because of muscle soreness or weakness, the vast majority are unaffected. There is something of a biological progression, from muscle soreness, through more severe muscle problems, to increased levels of creatinine kinase enzymes, to rhabdomyolysis, and even death from rhabdomyolysis (in about 1 in 15 cases).

Most of the spontaneous reports of rhabdomyolysis to the FDA were associated with cerivastatin, now withdrawn [1]. The problem with spontaneous reporting is that while it may identify cases, there is always uncertainty about denominators, so rates of adverse events are imprecise. Randomised trials are poor at finding rare but serious adverse events, because the events do not occur in sufficient numbers. Only 12 cases of rhabdomyolysis were reported in 30 RCTs reviewed [1].

One way of trying to overcome both these problems is by using large cohort studies, where people prescribed a drug, statins in this case, are enrolled in good databases that can identify cases of the adverse events examined. Such a cohort study on statins and rhabdomyolysis [2] is informative.

Study

This was a retrospective cohort study of patients in 11 US health plans providing pharmacy benefits, and with automated claims files covering prescription drugs, outpatient visits, and hospital admissions. Patients with a first prescription of statin or fibrate were entered, as long as there was no such prescription in the previous six months.

Potential cases of hospital admission for rhabdomyolysis were identified from records of members of the cohort using coded discharge diagnoses. Also used were claims for measurement of creatinine kinase within seven days of admission or discharge, or a discharge diagnosis of renal failure plus a creatinine kinase measurement.

Three assessors blind to statin or fibrate exposure status reviewed abstracts of medical records. Rhabdomyolysis was defined as severe muscle injury present at admission, plus a diagnosis of rhabdomyolysis or creatinine kinase more than 10 times the upper limit of normal. Severe rhabdomyolysis was defined as a serum creatinine kinase above 10,000 IU/L or more than 50 times the upper limit of normal.

Table 1: Rhabdomyolysis cases, rate, and NNH for different lipid-lowering treatments

Lipid-lowering drug	Number	Person years	Rhabdomyolysis cases	Rate per 10,000 patient years (95% CI)	One-year NNH
Atorvastatin, pravastatin, simvastatin	213377	203456	9	0.44 (0.2 to 0.8)	22,727
Cerivastatin	12695	7486	4	5.3 (1.5 to 14)	1,873
Gemfibrozil, fenofibrate	20485	10631	3	2.8 (0.6 to 8.2)	3,546

Results

The cohort included a quarter of a million people with 225,000 person years of monotherapy for statin or fibrate, and 7,300 years of combined therapy of statin plus fibrate. There was little information for fluvastatin or lovastatin, and these drugs were ignored in favour of the bulk of statin information on atorvastatin, pravastatin, and simvastatin. Fibrate information was much lower than that for statins, and included gemfibrozil and fenofibrate. Within the cohort there were 77,000 person years not exposed to lipid-lowering drugs, during which no cases of rhabdomyolysis were reported.

Thirty-one patients met the inclusion criteria for rhabdomyolysis. Seven of these were excluded because rhabdomyolysis occurred during a period when the prescription records showed that they were not exposed to a lipid-lowering drug. In each case their hospital records showed that they were taking a statin at the time of the event.

Of the 24 events remaining, there were 13 events on statin monotherapy, three on fibrate monotherapy, and eight cases with combined therapy with both statin and a fibrate. Various doses of each statin and each fibrate were being used for monotherapy and combined therapy. Three-quarters of the events were defined as severe rhabdomyolysis. Hospital stay was 1-11 days (average 6). Two patients underwent haemodialysis, and one died.

Monotherapy

There was no difference in rate of hospital admission for rhabdomyolysis between atorvastatin, pravastatin, and simvastatin. The combined event rate was 0.44 per 10,000 person years of exposure (Table 1), and the one-year number needed to harm (NNH) was 22,700. For cerivastatin, the

rate was about 10 times higher, with a NNH of 1,870. For fibrates the NNH was 3,550. Age over 65 years and having diabetes increased the risk of rhabdomyolysis with statin monotherapy, but duration of use made no difference to the event rate.

Combined therapy

Combined use of statin and fibrate increased the risk of rhabdomyolysis. With atorvastatin or simvastatin plus a fibrate the incidence rate was between 17 and 23 per 10,000 person years, about 40 times higher than with statins alone. The NNH for one year of therapy with atorvastatin, pravastatin, or simvastatin plus a fibrate to produce one case of hospital admission for rhabdomyolysis was 1,670. For a patient aged 65 years or older with diabetes treated with both a statin and a fibrate the NNH was 480.

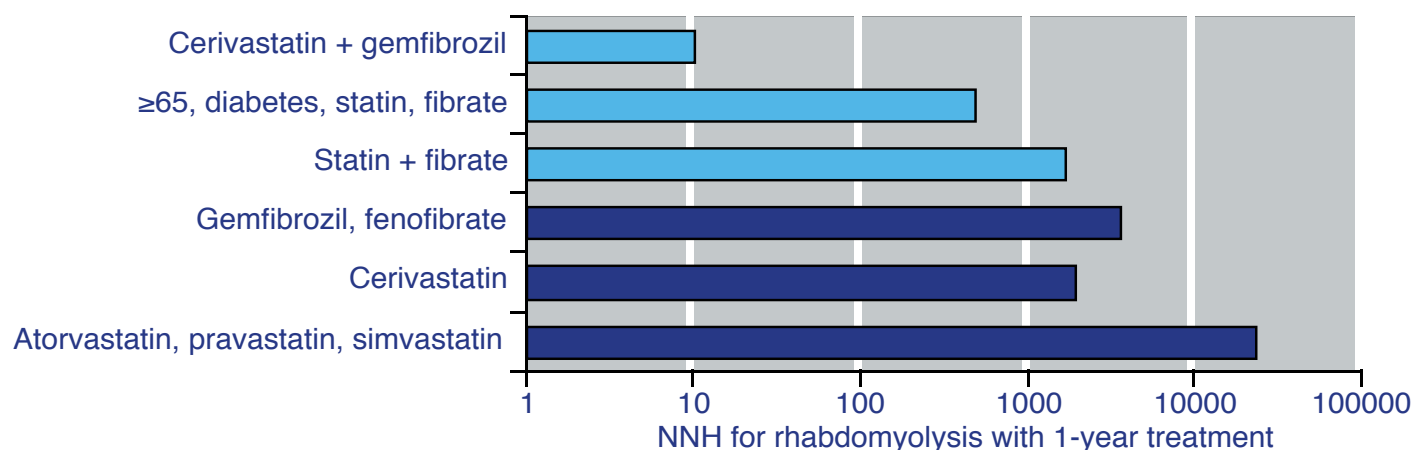
Combined use of cerivastatin plus gemfibrozil produced a rate of about 1000 per 10,000 person years, with an NNH of about 10.

Comment

The problems researchers face over rare but serious adverse events are clear here. Start with a quarter of a million patients and end up with only 24 actual events. Those 24 events include several drugs, at several doses, and given either separately or in combination. And while this is probably the best study of rhabdomyolysis with statins we have, even this has a problem. Seven cases occurred when patients were not on statins according to the prescription analysis, but were on statins according to the hospital records. Fortunately including or excluding the results made no difference.

Despite all these concerns we have some reasonably clear results. Rhabdomyolysis did not occur in the cohort when

Figure 1: NNH for rhabdomyolysis for different treatments, combinations, and conditions



they were not taking statins or fibrates, as best we can judge. Rhabdomyolysis did occur when they were taking statins or fibrates. We have a reasonable estimate of how frequently the events occurred, both in single and combined use (Figure 1). This allows an estimate of risk of rhabdomyolysis, which is really extremely rare in people taking the most commonly prescribed statins.

With fibrates, or combined therapy, or people more at risk, or with certain combinations (now impossible because one of the drugs has been withdrawn), the risks are higher, or were even common. What we also know is that the risk of dying was even lower. In the 225,000 person years of therapy, even including the withdrawn cerivastatin, only 31 cases occurred, and only 3 of those died. As 10 of the cases were associated with cerivastatin, it would be reasonable to estimate that risk of death with statin, fibrate or combination with drugs commonly prescribed is of the order of 1 per 100,000 per year, and is probably less common than that.

And finally

For those interested in such things, another study examined the history of cerivastatin and rhabdomyolysis [3]. It points out that information was available to company and FDA associating cerivastatin monotherapy and increased rate of rhabdomyolysis some while before this was disseminated.

References:

- 1 PD Thompson et al. Statin-associated myopathy. JAMA 2003 289: 1681-1690.
- 2 DJ Graham et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004 292: 2582-2590.
- 3 BM Psaty et al. Potential for conflict of interest in the evaluation of suspected adverse drug reactions. JAMA 2004 292: 2622-2631.

FOLATE IN PREGNANCY AND BREAST CANCER

Much media attention has been given to a possible link between folate use in pregnancy and breast cancer developing years later. This emphasises the problems of deciding whether there is a problem, and how much bigger the problem is with one intervention than another.

Study [1]

This is a follow up of a randomised trial conducted in the late 1960s where women were randomised to placebo (1971), 0.2 mg folate (488), or 5 mg folate (488) daily. Patient records were held by a registry, and the 210 deaths out of 2928 women randomised by 2002 analysed. All cause mortality, cardiovascular mortality, and all cancer and breast cancer mortality were separately analysed, both unadjusted and adjusted for maternal age, smoking, height, weight, and other variables.

Results

There were no statistically significant differences for any outcome between women who had taken 0.2 mg folate and those who had taken placebo.

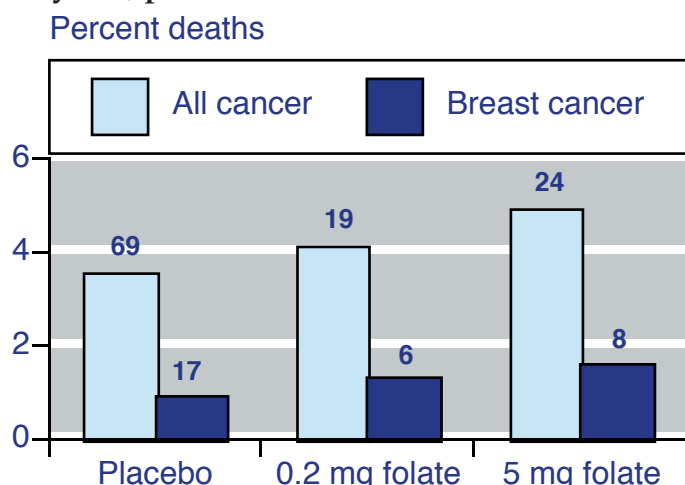
There was one statistically significant result for women who had taken 5 mg folate. All cause cancer deaths were more common, with 24 of 488 (4.9%) with 5 mg folate, and 69 of 1971 (3.5%) with placebo. The adjusted hazard ratio was 1.7 (1.06 to 2.7), but the unadjusted ratio had a confidence interval that included 1.

Results for all cause cancer deaths and breast cancer deaths are shown in Figure 1, together with the number of events. For breast cancer deaths, neither adjusted nor unadjusted hazard ratio had a confidence interval that included 1.

Comment

The authors of this study have linked folate intake in pregnancy and breast cancer mortality over the succeeding 35

Figure 1: Cancer and breast cancer deaths over 35 years, percent and number of cases



years. The title of the paper specifically makes the link: "Taking folate in pregnancy and risk of maternal breast cancer".

Yet there was no significant association between breast cancer mortality and folate, even with a 5 mg of folate, a dose about 10 times higher than that taken in pregnancy. Out of over 20 tests of significance, only one was statistically significant, about what we might expect by chance alone using 95% confidence. And the number of breast cancer events was only 14 with folate, and only six with 0.2 mg and eight with 5 mg (Figure 1).

So where is the news? What is the message? Is there any message from a study too small to detect anything, and in which nothing was detected? Bandolier has long been a supporter of a journal of negative results (maybe there is one), and perhaps that would have been the right journal for this paper.

Reference:

- 1 D Charles et al. Taking folate in pregnancy and risk of maternal breast cancer. BMJ 2004 329:1375-1376.

ANTIPSYCHOTICS AND SUDDEN CARDIAC DEATH

Sudden cardiac death has been reported with use of antipsychotics since the 1960s, though there have been few studies, and those we have were small and took little account of potential confounding factors. The evidence was therefore weak. A large case-control study from a high-quality database with full patient information [1] provides more information.

Study

A large Dutch electronic database of about half a million patients of 150 general practitioners provided the information. The records contain details on demographics, symptoms, diagnoses, and outpatient and hospital records, including tests, and drug prescriptions. All patients aged 18 years or older, except those with cancer, or those with death by suicide, formed the source population.

The study sought deaths occurring over six years (1995-2001), and experts blinded to patient exposure to antipsychotic drugs reviewed those that could possibly be regarded as sudden cardiac death. Sudden cardiac death was defined as death occurring within one hour after onset of acute symptoms, and if the death was recorded as sudden or acute cardiac death, or similar. If death was not witnessed, unexpected death of anyone seen in a stable medical condition less than 24 hours previously and with no evidence of a non-cardiac cause was used. For each case of sudden death up to 10 controls matched for age, sex, and practice were chosen.

Exposure was defined as current use, past use (longer than 30 days since end of last prescription), or non-use of antipsychotics. Type of antipsychotic, dose (DDD defined as recommended daily dose for an adult for schizophrenia), and duration of use were also noted. Known risk factors for sudden cardiac death were also collected from databases, and used in adjusting results.

Results

There were 582 cases of sudden cardiac death in a population of 250,000 adults over the period, an incidence of 1 per 1,000 per year. Controls (4,463) were available for 554 cases, of which 334 deaths were witnessed. The mean age was about 72 years and 60% were men. Known conditions and behaviours (heart failure, diabetes, smoking), and cardiovascular drugs were all associated with increased sudden cardiac death.

Figure 1: 95% confidence interval of the odds ratio associating antipsychotic use or dose with sudden cardiac death

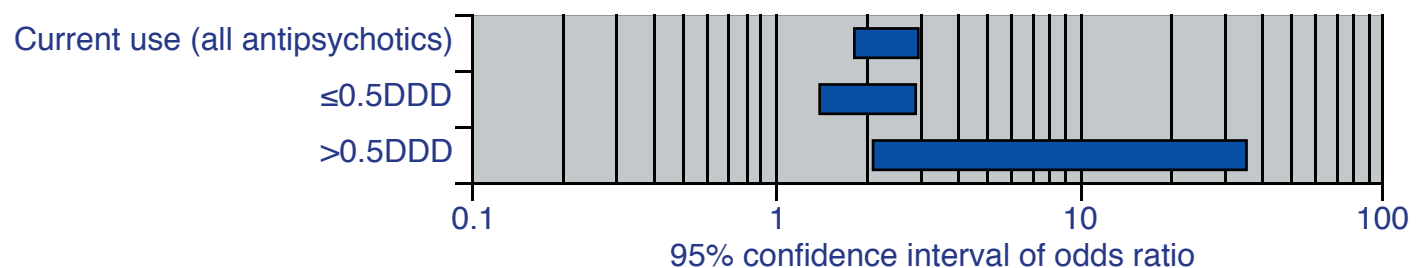


Table 1: Numbers of cases of sudden cardiac death and controls, and use of antipsychotic medicines

Use of antipsychotic medicine	Cases	Controls
Total patients	554	4463
Non-use	520	4352
Past use	15	74
Current use	19	37
Of which		
Butyrophones	12	13
Thioxanthenes	1	3
Lithium	3	9
Phenothiazines	3	12
Others (atypical)	2	7
At doses of		
≤0.5 DDD	14	33
>0.5 DDD	5	4

Most of the cases and controls did not use antipsychotics, or had done so in the past (Table 1). Only 19 (3.4%) cases and 34 (0.8%) controls were current users of antipsychotics, and in these the adjusted odds ratio for increased sudden cardiac death was 3.3 (95% CI 1.8 to 6.2; Figure 1). There was a somewhat higher association between use of antipsychotics and sudden cardiac death in witnessed deaths than unwitnessed deaths.

The numbers of users of different types of antipsychotics was small for each group (Table 1), but for users of older antipsychotics (haloperidol, for instance) the odds ratio was 7.3 (2.8 to 19) based on 12 cases and 13 controls using this group. No other group reached statistical significance, but based on small numbers of cases and controls using them. Higher doses were also associated with more frequent cardiac death (Figure 1), but only five cases and four controls were using doses above 0.5 DDD (Table 1). There was no difference between longer or shorter periods of use.

Comment

This is a detailed study, looking at a large population with excellent recording of patient details, and with a large number of sudden cardiac death events. Only 19 of these events occurred in people using antipsychotics, on which

the whole thesis rests. For any further analysis, by type of drug, by dose of drug, or by duration of use of drug, the numbers of cases mainly fall to single figures. Most of these analyses contain so few cases or controls that there must be a risk that they will be wrong just by the random play of chance.

So the best evidence we have is still limited, despite the quality and validity, and size of the population. We can

be reasonably sure than antipsychotics are associated in something like a threefold increase in sudden cardiac death, and perhaps that older antipsychotics may be worse. We cannot be sure that newer antipsychotics, or lithium, or phenothiazines, are without effect.

Reference:

1 SM Straus et al. Antipsychotics and the risk of sudden cardiac death. Archives of Internal Medicine 2004 164: 1293-1297.

QUINOLONES AND ACHILLES TENDON RUPTURE

Quinolone antibiotics have been associated with tendon problems since they were introduced in the 1980s. Case reports have indicated that Achilles tendon problems, and tendon rupture, may be a particular concern. How common these adverse effects may be, and whether they are associated with quinolone use, is answered by a case-control study using the UK general practice database [1].

Study

The UK general practice database is an electronic database with detailed information from a large number of practices and patients, with information on diagnoses, prescriptions, demographics, and hospital episodes. The population for this study was patients aged 18 to 95 years over the study period of 1989 to 1998.

Cases were people with a first time rupture of the Achilles tendon, with over 18 months of history in the database, and without a history of cancer, drug abuse, alcoholism, or hospital admission in the month before the event. Rupture due to major trauma (falling, car accident) was also an exclusion criterion. Indirect trauma associated with exercise, for instance, was not excluded. Controls were 50,000 randomly chosen people, with similar exclusion criteria applied.

For each case and control exposure to oral or parenteral quinolones was ascertained, defined as current (0-1 month), recent (2-6 months) or past (7-18 months). Type of quinolone and fraction of defined daily dose were recorded. Potential risk factors for Achilles tendon rupture were also recorded, including transplantation, arthritis, gout, systemic

corticosteroid use, and other factors. Risk factors found to be associated with Achilles tendon rupture were used to adjust the final odds ratio of association with use of quinolones.

Results

There were 1,367 cases of Achilles tendon rupture after a blinded review to ensure that inclusion and exclusion criteria were applied, and diagnosis appropriate. Between the cases and controls the major differences were the proportion of men (69% cases, 48% controls), corticosteroid use (11% cases, 4.6% controls), gout (3% cases, 1.5% controls), and transplant or dialysis (0.2% cases, 0.03% controls).

Most cases and controls had not used quinolones (Table 1), and any exposure to quinolones in the previous 18 months occurred in 4.5% of cases and 2.0% of controls. Only 14 cases were current quinolone users, and these were all aged over 60 years (Table 1).

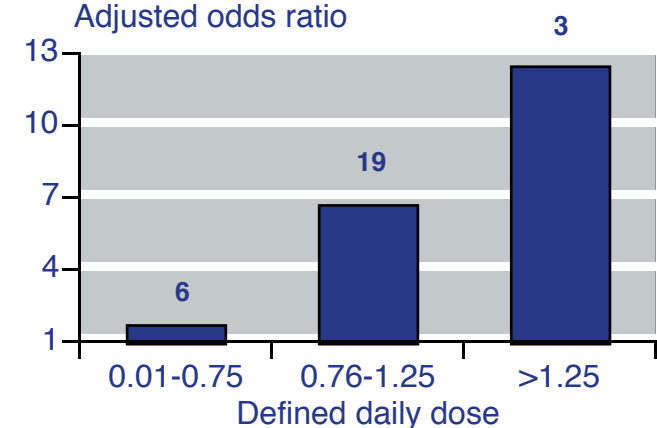
Four different quinolones were used (ofloxacin, ciprofloxacin, norfloxacin and nalidixic acid). Numbers of cases using individual drugs were small (six or fewer), but the highest adjusted odds ratios compared with nonusers were found for ofloxacin (OR 28) and norfloxacin (OR 14). For use of quinolones within three months, odds ratios were considerably higher with increasing DDD of quinolones (Figure 1), though only three cases and three controls used quinolones at the highest dose above 1.25 DDD.

Nine cases and five controls were currently using quinolones and were exposed to corticosteroids, and three were current-

Table 1: Number of cases with Achilles tendon rupture and controls, and use of quinolones

Use of quinolones	Cases	Controls
Total patients	1367	50000
Non-use	1305	48981
Past use (7-18 months)	24	605
Recent use (2-6 months)	24	315
Current use (0-1 months)	14	100
Of which		
Age <60 years	0	50
Age 60-79 years	11	41
Age ≥80 years	3	9

Figure 1: Adjusted odds ratio of association between Achilles tendon rupture and dose



ly using quinolones with recent exposure to corticosteroids. For these the adjusted odds ratio for Achilles tendon rupture was about 18 compared with no quinolone exposure, while for the four cases and 39 controls currently using quinolones and with no exposure to corticosteroids it was 5.3.

Comment

This is a detailed study, looking at a large population with excellent recording of patient details, and with a large number of Achilles tendon ruptures. Only 14 of these events occurred in people using quinolones, all aged over 60 years, and in nine of those there was concurrent use of corticosteroids, also known to be associated with Achilles tendon rupture. For any further analysis, by type of drug,

by dose of drug, or by duration of use of drug, the numbers of cases mainly fall to single figures.

What we can be reasonably sure of is that quinolone use in older people also taking corticosteroids has a large increased risk of Achilles tendon rupture. Larger doses probably carry a bigger risk. Most of the other analyses contain very few cases or controls, and there must be a risk that they will be wrong just by the random play of chance.

Reference:
1 PD van der Linden et al. Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking corticosteroids. Archives of Internal Medicine 2003 163: 1801-1807.

INTERVIEWS FOR DRUG EXPOSURE CAN BE INCORRECT

It is often the case that in epidemiological studies associating drug use to later outcome, drug use is determined by an initial interview. Patients are asked about the drugs they are taking, as well as many other factors, and these are then used to assess whether there is or is not an association between drug use and outcome.

Patients can be mistaken. Over time drug use might change, especially as patients get older and new conditions emerge and are treated. A new study [1] demonstrates that information from initial interviews can be incorrect, and may change the results.

Study

The study was of inhabitants of a suburb of Rotterdam aged 55 years or older living there in 1990-1993. All obtained prescription medicines from pharmacies sharing one automated computer system. Cohort members were from a previous study in this population concerning a link between calcium channel blockers and cancer.

This earlier study collected information on calcium channel blocker use from an initial interview. Pharmacy records were used to assess whether the information at the initial interview was correct according to prescriptions filled. Nonusers filled no prescriptions, non-chronic users filled less than 180 days of prescriptions, and chronic users filled at least 180 days of prescriptions.

Results

There were 2,487 persons with a median follow up of 7.6 years. Users of calcium channel blockers (by interview) were much more likely than declared nonusers to have ischaemic heart disease, stroke, or angina, and to be using diuretics, β -blockers, ACE inhibitors or statins.

At baseline, 206 persons said they were using a calcium channel blocker, and 2,281 said they were not (Table 1). Of the declared users, three did not have a prescription filled, and eight were non-chronic users. Of the declared nonusers, 204 were or became chronic users, and 150 non-chronic users.

Table 1: Use of calcium channel blockers by initial interview and by pharmacy records. Shaded areas show complete agreement

User status by interview	Total	Prescription records		
		Chronic	Non-chronic	Nonuser
User	206	195	8	3
Nonuser	2281	204	150	1927

The association between calcium channel blocker use and cancer using baseline assessment at interview had a relative risk of 1.4 (95% CI 0.9 to 2.1). The age and sex adjusted relative risk based on chronic exposure by pharmacy prescriptions was lower, at 0.9 (0.6 to 1.2). Use of interview data overestimated the risk by about 36%.

Comment

There was a clear misclassification of use of calcium channel blockers between initial interview and pharmacy prescription records. It could be argued that in this case it made no difference, because neither with interview nor pharmacy records was there a significant association between calcium channel blockers and cancer.

But the study serves to make a point: that there are potential biases that can occur in observational studies, and we probably know neither what they all are, nor therefore can we adjust for them all. Of course, if we have a large study, with lots of events, and big differences it probably makes no big difference. But if we have bare statistical significance, or small effects, or small numbers, then we should be cautious.

Reference:
1 AB Beiderbeck et al. Misclassification of exposure is high when interview data on drug use are used as a proxy measure of chronic use during follow-up. Journal of Clinical Epidemiology 2004 57: 973-977.

PAIN IN THE KNEE

Most people working in primary care are aware that knee pain is common, especially in older people. Much is mild, and has little impact on how those with knee pain get on with their lives. But, as with most conditions, there is a gradation in severity, so that some have more pain, or are disabled, some should be getting specialist advice, and some of those perhaps need a joint replacement. Knowing the numbers would be helpful in planning services, and a Manchester study [1] provides them.

Survey

The survey was conducted in an urban part of Manchester. Populations were divided into eight groups defined by age and sex, and about 250 people in each group sampled in each medical practice, with 5,600 questionnaires sent initially. This first phase questionnaire asked about musculoskeletal symptoms, pain in various sites for more than one week in the past month, demographics, and employment status. This questionnaire also included a health assessment questionnaire to help define disability.

A second questionnaire was sent to those reporting knee pain (not multiple pain). This asked about severity, chronicity, and primary care and hospital consultations for knee pain. A sample of responders was invited for examination.

Results

Response rates at all levels of the study were generally good, at about 80% or above. Overall prevalence of knee pain was similar in adult men and women at about 19%, but was higher than this in older persons (Figure 1 for women and Figure 2 for men). Knee pain plus disability defined as a health assessment questionnaire score of 0.5 or above was lower (Figures 1 and 2), at about 6% overall. Knee pain plus disability defined as work disability in those aged below 65 years was 2.8%.

Responses to the second questionnaire were similar between women and men, and showed the same gradation with age. Overall, 12% of adults had knee pain that was moderate or severe, 9% had knee pain of more than five years, and 3.4% had moderate or severe pain and disability.

Predictors of knee pain were sought. Factors associated with increased knee pain were higher BMI (Figure 3), increasing social deprivation (Figure 4), and South Asian ethnicity. A significant proportion of knee pain could be ascribed to being overweight or obese. Of all knee pain, this was 21%, and up to 37% for moderate or severe pain with disability. Most of this came from being overweight (BMI 25-30), not being obese.

From an analysis of 66 patients seen by a consultant rheumatologist it was estimated that 4.5% of the adult population needed specialist treatment, most (2.8%) for orthopaedics. The unmet need was about twice the level of need currently being met. In a practice population of 10,000 adults, this unmet need amounts to 320 patients.

Figure 1: Knee pain reported by women, all reported pain, and pain plus disability

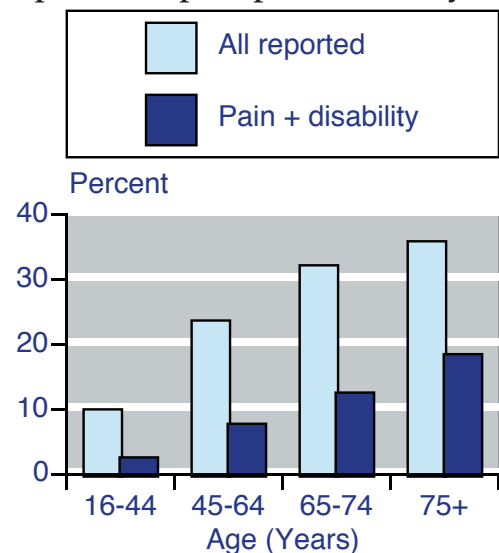


Figure 2: Knee pain reported by men, all reported pain, and pain plus disability

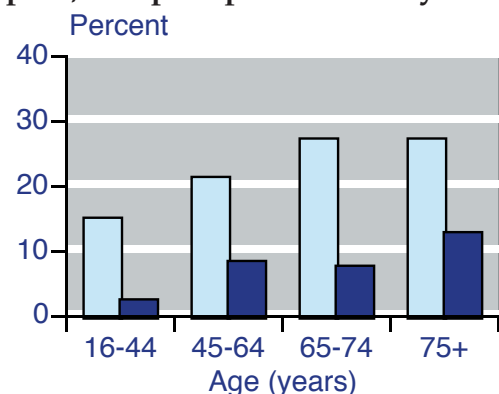


Figure 3: Adjusted odds ratio for knee pain and BMI

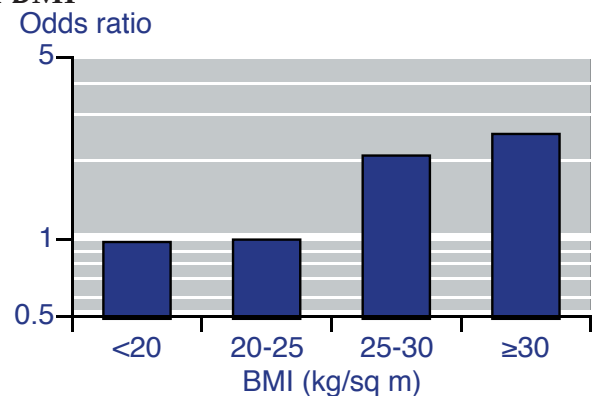
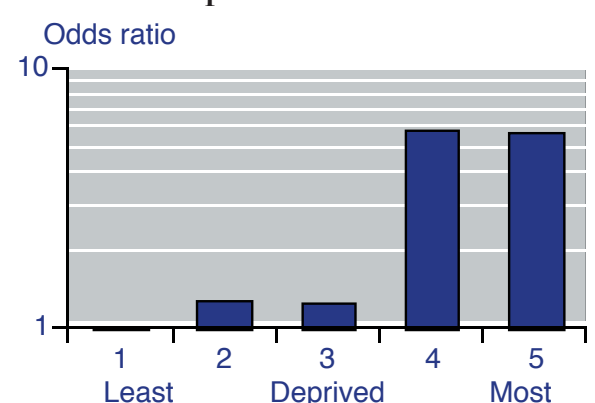


Figure 4: Adjusted odds ratio for knee pain and Townsend deprivation index



Comment

When planning services, it always helps if you have some idea of what you need to provide. A simple sentence this, but one for which it is often desperately difficult to provide numbers. For knee pain in the community, we have some numbers to help.

Bandolier 103 reported a survey showing a large unmet need for hip replacements, and the present survey shows another large unmet need for knee pain, probably including replacement. But it also demonstrates that there is an opportunity to reduce the burden of knee pain, by showing the link with being overweight. Reducing excess weight in the community will have many paybacks, not just heart disease and cancer, but also in a reduced requirement for specialist services for musculoskeletal conditions.

Reference:

- 1 R Webb et al. Opportunities for prevention of clinically significant knee pain: results from a population-based cross sectional survey. *Journal of Public Health* 2004 26: 277-284.

BOOK REVIEWS

NHS plc. Allyson Pollock. Verso, London, New York, 2004, ISBN 1-84467-011-2 260pp; £15.

Though not badged as such, Allyson Pollock has written a history of the National Health Service in the UK, concentrating on the latter half of its 50 years or so of life. She documents increasing privatisation, regulation, and prescription, leading, she thinks, to its eventual demise as a cradle to grave service with equal access to all. She doesn't like the change.

While there is little doubt that this is a partisan view, even those with a pro-market view of the world might understand why market forces and healthcare organisation do not make good bedfellows. Bandolier 103 and 107 contained reviews showing how for-profit organisations did less well than not-for-profit organisations in the USA. One is unaware of any review with an opposite finding.

Large organisations may be inherently difficult to manage, and have patchy funding or quality of performance, but revolution might not be the answer, attractive though it may seem. Revolution, like Saturn, may devour its children, and every revolutionary ends up either by becoming an oppressor or a heretic. Try starting with the most important chapter, the penultimate one about overcoming opposition. It reads more like something from 18th century France or 20th century Russia or Germany than the urbane and tolerant Britain in which we used to live.

Revolving doors would have made a good chapter heading. Supporters of change frequently reappear in new guises, while opposers disappear. Scary stuff. But perhaps it is all the product of too fervent an opposition, too fertile an imagination. Then read the other chapters and see what you think.

It could be better. Bandolier would have liked to have seen more evidence about fraud and distortion in for-profit healthcare systems, and more evidence about poorer performance by for-profit over not-for-profit organisations. And you need to have a more than the usual number of neurones plugged in to get the best of it, because it is intense.

This is a book that should be read by every NHS employee, and every patient or prospective patient, and there are lessons for those outside the UK as well.

The whole story: alternative medicines on trial. Toby Murcott. Macmillan, Basingstoke & New York, 2005, ISBN 1-4039-4500-4 167pp; £16.99

This is a fun little book about complementary and alternative therapies. It is not about what works, or what does not work, and remains impishly neutral. Perhaps that reflects how Toby Murcott, a biochemist and science journalist feels after speaking to experts on different sides of the argument, and reading around the subject.

He gets quickly to the point: that complementary therapy is about making people with chronic conditions feel better (about themselves?), and not about curing the sick. He points out that complementary therapies never have been able to help with major problems, whether infectious diseases or trauma. It didn't, and couldn't, help a Bandolier uncle who died in the pre-antibiotic era with blood poisoning from a simple foot injury.

Murcott's suggestion is that chronic conditions are not modern medicine's strong suit, and that it is the time therapists have that can make a difference. He delves into evidence, and trials, and systematic reviews, and placebo effects, and whether any of these are relevant to complementary therapies. But when so many people use it, and when the monetary value is \$60 billion globally and rising fast, the questions have to be asked.

This little book doesn't really come to any particular conclusion, and is no worse for that. Whichever side of the argument you start, you will shout "rubbish" at some point, but at least you will have been exposed to a different point of view, and be no worse for that. The book ends with an Iain Chalmers quote about humility, never a bad thing in as complicated an area as medicine.

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